Revision of EPA 1-liners pertaining to the EPA Memorandum (2/16/89) was performed (12/20/89) by M. Silva.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

AMITROLE

SB 950-006, Tolerance # 50137
Chemical Code #: 000020

November 10, 1986
Revised 7/3/87, 10/17/88 and 5/16/89

I. DATA GAP STATUS

Chronic Rat:	No data gap, possible adverse effect
Chronic Dog:	Data gap, inadequate studies, possible adverse effect indicated
Onco Rat:	No data gap, possible adverse effect
Onco Mouse:	No data gap, possible adverse effect
Repro Rat:	Data gap, inadequate study, possible adverse effect indicated
Terato Rat:	No data gap, no adverse effect
Terato Rabbit:	No data gap, possible adverse effect
Gene Mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA Damage:	No data gap, possible adverse effect
Neurotox:	Not required at this time

Note: Toxicology One-Liners are attached

**Indicates acceptable study
Bold face indicates possible adverse effects
File Name: T890516
Reviews by J. Gee and J. Parker; Toxicology Summary revised by J. Gee, 10/17/88 and 5/16/89.
Record numbers rectified through volume 049, # 073633.

"Amitrole: Pesticide Registration Standard and Guidance Document," US EPA, March, 1984 - see 50137-013.

II. TOXICOLOGY SUMMARY

Preliminary discussion: A document submitted in Volume 50137-004, dated October, 1983, discusses the effect of Amitrole on the thyroid, giving a mechanism of action in which thyroid peroxidase is inhibited making the chemical goitrogenic. Histological changes occur early and the thyroid becomes enlarged. The document gives 2 ppm in the diet for 13 weeks as the lowest subchronic (13 weeks) dose in rats affecting thyroid function with 0.5 ppm as a NOEL. The histological changes are stated to be reversible. In long-term exposures, hypertrophy and hyperplasia of the thyroid occur and eventually, rats develop neoplasms, "presumably" by prolonged and excessive TSH stimulation. The document states that hamsters are less sensitive than rats and mice. In dogs, thyroid changes occurred but tumor formation did not occur in the studies as conducted. Gee, 7/7/87

SUMMARY OF CHRONIC/ONCOGENICITY STUDIES: The thyroid is clearly identified as the target for toxicity. **The requirements for chronic/oncogenicity studies in the rodent are fulfilled by the collective data** with the submission of 068919 in 044. Gee, 10/17/88.

044 068919 Supplement to 002352, 002353 and 002354, oncogenicity studies in the mouse, hamster and rat conducted at Bayer, reports 8490, 7521 and 8450, respectively. Submission consists of individual data for body weight, food presentation, actual content and stability in the diet over seven days. Purity of lot 143 was 96.4 to 97.1% on three dates over 2 years. Submission of these data upgrade the collective data for chronic/oncogenicity feeding studies in rodents to acceptable status with the thyroid identified as the target organ. Gee, 10/17/88.

COMBINED RAT

005 002351 "Lifetime Feeding Study of Amitrole in Fischer 344 Rats." (Food and Drug Research Lab, Report no. 5651, 8/7/81) Amitrole, 94.59%; fed in the diet at 0, 1, 3 or 10 ppm alternate weeks from weeks 1 through 39 and changed to 20, 60 or 200 in alternate weeks, 40 - 115; also, 5 ppm, weeks 1 - 39, changed to 100 ppm, weeks 40 - 115 for males and weeks 40 - 119 for females; 75/sex/group; histology on two high dose groups, all animals, plus controls; thyroid neoplasms at 100 ppm and 200 ppm; **UNACCEPTABLE** (originally reviewed as acceptable with minor variations but reconsideration found the study unacceptable based on dosing regimen, no analysis of diet). Apparent NOEL = 60 ppm (thyroid neoplasms). J Gee, 2/28/85 and 10/2/85.

026, 027 and 028 035196, -97 and -98 (Food and Drug Research Labs, 8/7/81) More complete version of 005 2351 (see above). J Gee, 10/2/85.

022-025 035192 - 035195 "Evaluation of the Chronic Inhalation Toxicity and Carcinogenicity of Amitrole in Rats." (Food and Drug Research Laboratories, Report no. 5821, 1/13/83). Amitrole, 94.59%, given by inhalation for 5 hours/day, intermittent exposure in weeks 1-13, 40-52 and 78-90; 75/sex/group at 0, 0.05 or 0.50 mg/liter; actual concentration was measured; problems with temperature elevation caused mortality in week 51; NOEL < 0.02 mg/liter (actual); thyroid/pituitary effects with hyperplastic and neoplastic lesions; **UNACCEPTABLE** (dosing regimen designed to study reversibility; high mortality at high dose and only two exposure rates; inadequate tissues for histopathology). J Gee, 10/2/85.
EPA One-Liner: Supplementary. Onco NOEL < 0.05 mg/L (LDT) (increase in thyroid tumors).

CHRONIC RAT

004 002331 "Long-term Exposure Studies - Oral Exposure Studies with Rats - Two-year Chronic Feeding (Oncogenicity) of Amitrole." (Union Carbide, 1983) Review of several studies in rats with Amitrole, including the one by Hazleton (no. 035188) below. Also included is a reference to a study conducted in the USSR in 1969 in which 60 to 70 mg/kg b.w./day caused thyroid and liver tumors. A study published in the J. Natl. Cancer Inst. 57:861-864 (1976) reported all rats exposed to about 400 mg/kg/day developed goiters and about 12% developed benign thyroid tumors. A study conducted by Bayer, Report No. 8450, 1979, in which rats were fed 1, 10 or 100 ppm for life, indicated that at 100 ppm, thyroid cysts were common and both benign and malignant tumors occurred but no liver tumors. Record no. 2351 is also summarized.

For mice, no. 2352 is included and, for hamsters, a study by Bayer in 1979 in which golden hamsters were fed 1, 10 or 100 ppm with no benign or malignant tumors or histopathological changes.

For dogs exposed for 37 or 50 weeks to 300 to 500 mg/kg/day in drinking water, the thyroids showed histological changes but no tumors (publication in Japanese). Hazleton's 1958 study (no. 35188) is also summarized.

UNACCEPTABLE. J Gee, 3/8/85.

004 002334 "Long-Term Exposure Studies - Exposure by Injection - Rats - To Detect Tumors." (Union Carbide, 10/83) Summary paragraph. Amitrole, no purity stated, injected subcutaneously in rats at 125 mg twice weekly for 11 months, caused "high incidence" of liver and thyroid tumors. From a publication in Gig. Trud. Prof. Zabol. 6:48-51 (1962). A later study (1969) with injections for 6 months was negative. **UNACCEPTABLE**. J Gee, 11/7/86.

003 910942 "Two-Year Chronic Dermal Toxicity Study with Amitrole 3-At in Albino Rats." (IBT Report no. A7639, 3/72) Assume invalid IBT study. Not listed by EPA.

004 002332 (Union Carbide, 10/83) Summary paragraph of 910942, IBT study. J Gee, 11/7/86.

020 035188 "Two-Year Chronic Feeding - Rat (Final Report)- Aminotriazole (3-Amino-1,2,4-Triazole)." (Hazleton Labs, 1/2/59) Amitrole (Amchem), no purity stated, fed to 35/sex/group at 0, 10, 50, 100 or 500 ppm for 104 weeks; high dose was terminated after 26 weeks; NOEL = 10 ppm; thyroid changes were seen early in study at 13 weeks when 5/sex/group were sacrificed and the observation continued at subsequent times; **UNACCEPTABLE** (low number of starting animals, no description of test article, no analysis of diet, no good summary tables, inadequate tissues for histopathology). Thyroid effects at 50 and 100 ppm and fatty liver changes at 100 ppm. J Gee, 10/1/85.

EPA One-liner: Oncogenic NOEL = 50 ppm, onco LEL = 100 ppm (adenomas), NOEL = 10 ppm, LEL = 50 ppm (histological changes in thyroid). Invalid.

002 910954 Discussion of 35188. J Gee, 2/28/85.

035 050767 Progress reports with additional data for 035188.

003 910939 IBT study (1972) not listed by EPA so assume invalid. Inhalation study in rats. J Gee, 2/27/85.

004 002333 (Union Carbide, 10/83) Summary paragraph of 910939, IBT study, 1972. J Gee, 11/7/86.

CHRONIC DOG

004 035701 "Long-term Exposure Studies - Oral Exposure Studies with Dogs Dosed with Amitrole." (Union Carbide, 10/83), from Nagoya Shiritsu Daigaku Igakki Zaschi, 1975, in Japanese. Amitrole, no purity stated; one paragraph summary in which registrant states thyroid goiters were found at 300-500 mg/kg body weight per day in the drinking water at 37 to 50 weeks. **UNACCEPTABLE** (insufficient information for assessment). J Gee, 3/8/85.

020 035189 "Chronic Oral Administration - Beagle Dogs (Final Report) - 3-amino-1,2,4-triazole." (Hazleton Labs, 12/1/58) Amitrole, no purity stated, given in gelatin capsules for one year to Beagle dogs at 0, 0.25, 1.25, 2.5 or 12.5 mg/kg, 6 days/week; 2/sex in control, 1-3/sex in treatment groups; NOEL > 12.5 mg/kg/day; **UNACCEPTABLE** (dose selection, inadequate animal number, too few tissues for histopathology); no adverse effect reported. J Gee, 10/1/85.
EPA 1-liner: EPA does not require this type of study for Amitrole (2/16/89).

035 50768 Individual histopathology data for 035189.

A letter, dated April 5, 1989, in document 50137-049, from Inge Davis of Rhone-Poulenc indicates a new chronic feeding study in the dog will be conducted. Gee, 5/16/89.

ONCOGENICITY, RAT

008 002354 "Aminotriazole (Amitrole) Cancerogenesis Test with Oral Administration to Rats." (Bayer, Report no. 8450, 6/11/79) Amitrole, 96 - 97%, fed in the diet to 75/sex/group at 0, 1, 10 or 100 ppm; mortality increased at the high dose; increase in thyroid tumors at 100 ppm; NOEL = 10 ppm (thyroid effects). Initially reviewed as acceptable but status changed to **UNACCEPTABLE** (no analysis of diet, no individual data (b.w., food consumption, time to death). Record 068919 in 044 contains purity, diet analysis and stability data and individual body weights. For summary statement on chronic/oncogenicity studies in rodents, see above. J Gee, 3/1/85 and 10/17/88.
EPA One-Liner: Core Minimum. Onco NOEL = 10 ppm (increased incidence of thyroid and hypophyseal tumors).

ONCOGENICITY, MOUSE

003 910944 "Tests of Mice for Evaluating Carcinogenicity." Publication from Toxicol. Appl. Pharmacology 9:583-596 (1968). Amitrole, analytical, given by subcutaneous injection to 50/sex/group, single injection of 10 mg or weekly skin applications of 0.1 mg or 10 mg, in 0.2 ml acetone. No evidence of tumors is reported. **UNACCEPTABLE**. J Gee, 2/27/85.

004 035699 "Long-Term Exposure Studies - Oral Exposure Studies with Mice and Hamsters - Incidence of Thyroid and Liver Tumors in Mice Dosed with Amitole Throughout Their Lives." (Union Carbide, 10/83) Summary only of publication in J. Natl. Cancer Inst. 42:1l01-1114 (1969) which suggests an adverse effect to pituitary at 100 ppm (congestion), increased thyroid tumors at 2,192 ppm in a long-term feeding study. **UNACCEPTABLE**. J Gee, 3/8/85.

006 002352 "Aminotriazole (Amitrole) Carcinogenesis Study with Oral Administration to Mice." (Bayer, Report no. 8490, 7/17/79) Amitrole, 96 - 97%, fed to 75/sex/group of NMRI mice at 0, 1, 10 or 100 ppm for a total of 1,028 days; no adverse effect reported; onco NOEL $\geq$ 100 ppm; **UNACCEPTABLE** (dose selection with no m.t.d., no hematology/no clinical chemistry - a minor deficiency for an oncogenicity study). See summary statement below. Record 068919 in 044 contains purity, diet analysis and stability data and individual data for body weights and terminal fate. J Gee, 2/28/85.

EPA One-Liner: Core Minimum. Onco NOEL > 100 ppm (HDT).

ONCOGENICITY, HAMSTER

007 002353 "Aminotrizaole (Amitrole) Carcinogenicity Study on Orally Dosed Golden Hamsters." (Bayer, Report no. 7521, 5/16/78) Amitrole, 96 97%,stated, fed in the diet to golden hamsters, 76/sex/group, at 0, 1, 10 or 100 ppm; histology on dead animals with increased mortality at 100 ppm; no onco adverse effect reported at 10 ppm; NOEL = 10 ppm (decreased body weight, food consumption and increased mortality); initially reviewed as acceptable but changed to **UNACCEPTABLE** (histopathology on dead or moribund animals, no analysis of diet, missing individual data). See summary statement below. Record 068919 in 044 contains purity of test material, diet analysis and individual data for body weight and terminal fate. J Gee, 3/1/85 and 10/19/88.
EPA One-Liner: Core Minimum. Oncogenic NOEL > 100 ppm (HDT). Systemic NOEL = 10 ppm (reduced survival time).

004 035700 (Union Carbide, 10/83) Summary of 007 002353. Summary claims no oncogenic effect. J Gee, 3/8/85.

SUPPLEMENTAL STUDIES

043 068918 "Goitrogens and Thyroid Follicular Cell Neoplasia: Evidence for a Threshold Process." (Publication in Regulatory Toxicology and Pharmacology 8: 102 - 119 (1988) by Paynter, O. E. et al.) Amitrole (aminotriazole) is one of the compounds discussed as goitrogenic in rodents. The LEL and the NOEL in the Wistar rat are stated as 5.0 and 0.5 mg/kg/day, as 1.5 and 0.15 mg/kg/day for the NMRI mouse and as 0.01 and "-" for the golden hamster - data from the literature. In the study cited, amitrole showed no oncogenic effect in the mouse or hamster but increased benign and malignant thyroid and pituitary neoplasms at 100 ppm in the rat. The NOEL for thyroid function in the rat and mouse was 10 ppm. From other publications, the mechanism of action for amitrole is stated to be consistent with inhibition of thyroid peroxidase, interfering with iodination of tyrosine in thyroglobulin. Data on neoplastic effects are from Steinhoff et al, Toxicol. Appl. Pharmacol. 69: 161-169 (1983). The authors of # 068918 suggest the prolonged stimulation of the pituitary/thyroid axis results in hyperplasia which may progress to neoplasia. The hyperplasia is reversible prior to induction of neoplasia. **SUPPLEMENTARY.** Gee, 10/17/88.

045 070409 "FAO Plant Production and Protection Paper - Pesticides Residues in Food - 1977 - Amitrole" Summary of several mutagenicity studies stated to be negative. A 30 - 70 week study in Wistar rats given 2500 ppm in drinking water resulted in the development of goitre in all animals and cholangiofibrosis in the liver in 2 animals. In 4 short term studies, ^{131}I uptake was measured at 0, 2, 20, 50, 200 and 500 ppm in the diet for 6 - 13 weeks. A marginal effect was seen at 2 ppm. No data. **SUPPLEMENTARY**. Gee, 10/19/88.

045 070410 "WHO Pesticide Residues Series, No 4 - 1974 Evaluations of Some Pesticide Residues in Food: Amitrole." Review of studies conducted with amitrole. Amitrole was excreted by rats in the urine within 24 hours. Amitrole depressed catalase and peroxidase activity in various tissues of rats. A summary of a study in two strains of mice given 1000 mg/kg from day 7 - 28 and 2192 ppm in the diet thereafter states hepatomas were found in 67/72 animals (both sexes) and carcinoma of the thyroid in 67/71. Other studies were also summarized with thyroid and liver findings. Mutagenicity studies were negative in yeast, bacteria and rat bone marrow. In a reproduction study in rats fed 0, 25, 100, 500 or 1000 ppm, the number of pups born and pup survival were reduced at 500 and 1000 ppm. At 100 ppm, all animals had thyroid hyperplasia with the incidence "sporadic" at 25 ppm. Amitrole had no effect on development of fetuses in rats up to 100

mg/kg/day. A number of short-term studies are also included. Dermal application of 2.4 mg/kg for 30 minutes weekly over 23 months did not result in any findings. An inhalation study at 2 mg/l of air, head only exposure, for two years with rats was negative for liver and thyroid changes. **SUPPLEMENTARY.** No data. Gee, 10/19/88.

045 070411 "Effect of Aminotriazole on Thyroid Function in the Rat." (Publication in Toxicol. Appl. Pharmacol. 13: 271 - 286 (1968), M. J. Fregley) Aminotriazole, fed in the diet to male rats; three experiments - 1) fed at 0, 2, 10 or 50 ppm for 13 weeks; 2) 0, 0.025 or 0.50 ppm in the diet to 10 males/group; 3) 0, 0.15 or 0.78 mg/kg ip. Radioactive iodine was injected and thyroid uptake measured as a function of time by a scintillation detector. A minimal effect was found at 2 ppm with reduced protein-bound iodine concentration and reduced uptake of radioactive iodine by the thyroid. The author concluded the dose affecting the thyroid of male rats was between 0.5 and 2 ppm. **SUPPLEMENTARY**. Gee, 10/19/88.

REPRODUCTION, RAT

004 035702 "Teratogenicity and Reproduction: Reproduction - Rats (Amitrole)." (Union Carbide, 10/83) Amitrole, no purity stated; summary only of study in rats; registrant's summary of publication in Toxicol. Appl. Pharmacology 26:118-129 (1973), states litter size reduced at 500 and 1,000 ppm, post-natal survival reduced at 1 week at 500 and 1,000 ppm and at weaning at 1,000 ppm; **UNACCEPTABLE** (insufficient information for assessment). J Gee, 3/8/85.

A letter, dated April 5, 1989, in document 50137-049, from Inge Davis of Rhone-Poulenc, indicates a new rat reproduction study will be conducted.

TERATOLOGY, RAT

004 002347 "Teratogenicity and Reproduction-Rats." (Union Carbide, 10/83.) Very brief summary of several publications with no data; States no effect at 400 and 1,000 mg/kg/day. From Zbl. Vet. Med. A. 14:469-486 (1967). Summary of another publication (Anat. Rec. 145-284 (1963)) in which rats were exposed during pregnancy to 0.4 to 90 mg/kg/day in drinking water states slight histological changes in thyroid at all doses in fetuses sacrificed at birth, being greatest at the high dose. **UNACCEPTABLE**. J Gee, 2/27/85.

** 031 & 032 045709 & 045710 "Teratogenicity Evaluation of Aminotriazole Technical Administered by Gavage to CD Rats." (Union Carbide, Bushy Run Research Center, Report no. 49-45, 5/29/86) Aminotriazole Technical, 91.83%; gavage on days 6-15 of gestation at 0, 100, 500 or 1,000 mg/kg/day. Post-natal segment evaluated litters to weaning. Maternal NOEL = 100 mg/kg/day (decreased weight gain and food consumption during gestation and increased thyroid weights in dams at both gestation day 21 and post-natal day 21 sacrifice). Developmental NOEL = 500 mg/kg/day (decreased mean fetal weight at day 21 gestation). Study complete, **ACCEPTABLE** and no indication of an adverse effect. J A Parker, 11/3/86.
EPA 1-liner: Core Minimum.

TERATOLOGY, RABBIT

**** 033 045711** "Teratogenicity Evaluation of Aminotriazole Technical Administered by Gavage to New Zealand White Rabbits." (Union Carbide, Bushy Run Research Center, Report no. 49-66, 5/30/86) Aminotriazole Technical, 91.83%; administered by gavage on days 6-18 of gestation at 0, 4, 40 and 400 mg/kg/day; Maternal toxicity NOEL = 4 mg/kg/day (abortions and decreased weight gain); Developmental Toxicity NOEL = 4 mg/kg/day (increased incidence of structural changes);

Study complete; **ACCEPTABLE.** Possible adverse effect due to frequency and severity of defects. J A Parker, 11/5/86.
EPA 1-liner: Core Minimum.

041 067210 "Percutaneous Teratology Study with Amitrole Technical in Rabbits." (Hazleton Laboratories America, WI, HLA 6224-107, 3/11/88) Amitrole, technical, lot no. CFPI 232, 93.9% by analysis; 18 artificially inseminated Hra:(NZW)SPF rabbits per group were treated at 0 (water), 1.0, 1.5 or 2.0 g/kg/day, days 7 - 19 of gestation, 6 hours per day by dermal application, in water; at 2.0 mg/kg/day, food consumption and body weights were decreased and anorexia and thinness were noted - controls also lost weight after collared; dermal irritation (erythema and edema) was increased in a dose-related manner; external fetal observations of domed head, omphalocele, carpal and tarsal flexure were present at 2.0 g/kg, soft tissue findings of hydrocephaly, anencephaly, dilated lateral ventricles and others also at 2.0 g/kg, reduced fetal weight at 2.0 g/kg; maternal NOEL = 1.5 mg/kg/day (skin irritation, decreased food consumption associated with "thinness"), developmental NOEL = 1.5 g/kg/day by the dermal route (observations at 2.0 not noted in other groups); **INCOMPLETE** (no analysis of dosing solution included), **SUPPLEMENTARY DATA.** Aborted fetuses not examined. Possible adverse effect because of seriousness of observations in fetuses without significant systemic maternal effects. Without measurement of blood levels of amitrole, difficult to compare with results by oral route. Gee, 10/14/88.

TERATOLOGY, MICE

004 002346 "Teratogenicity and Reproduction: Teratogenicity - Mice." (Union Carbide, 10/83) Summary paragraph of publication in Arch. Toxikol. (Berlin) 33:41-48 (1974). Radio-labelled amitrole given to pregnant mice in drinking water at doses of 500, 1,000 to 5,000 ppm, resulted in reduced body weight and under-developed fetuses but no malformations. **UNACCEPTABLE**. J Gee, 11/7/86.
EPA one-liner: Invalid. Teratogenic NOEL => 500 ppm (HDT), systemic NOEL = 500 ppm (decreased maternal weight gain).

MUTAGENICITY, GNMU

004 002342 (Union Carbide, 10/83) Summary paragraph of published and unpublished reports on bacterial systems, primarily Salmonella, indicating negative results. **UNACCEPTABLE.** J Gee, 2/27/85.

004 002343 (Union Carbide, 10/83) Summary paragraph of study showing negative results in Aspergillus nidulans for point mutation (Mutation Research 46:395-402 (1977)). **UNACCEPTABLE.** J Gee, 11/7/86.

004 002344 (Union Carbide, 10/83) Summary paragraph on negative results in sex-linked recessive lethal assay in Drosophila from Mutation Res. 40: 185-190 (1976). **UNACCEPTABLE**. J Gee, 11/7/86.
EPA 1-liner: Unacceptable.

019 035186 "Mutagenic Evaluation of Compound 3-Amino-1,2,4-triazole (99.4%)-Reverse Mutation Assay in Saccharomyces cerevisiae (Strain D4) and Salmonella typhimurium." (Litton Bionetics, Report no. 2547, 8/14/75) Amitrole, 99.4%, tested with Salmonella strains TA1535, TA1537 and TA1538 with activation preparations from mouse, rat, monkey liver, lung and kidney; testing in spot test at 0 or 100 ug/plate, duplicate plates, no repeat trial; no mutagenic effect reported; **UNACCEPTABLE** (single concentration with no justification of selection, not all strains). J Gee, 10/1/85.

EPA 1-liner: Unacceptable.

019 035185 "Microbial Mutagen Assays with Amitrole." (Gibralter Biol. Labs, NJ, for Food and Drug Research Labs, Report no. 7515, 9/12/77) Amitrole, no purity stated, tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 at 0, 100 or 1,000 ug/plate, duplicate plates, disk assay, no repeat trial, with activation only; no increase in reversion rate reported; **UNACCEPTABLE** (no justification for 1,000 ug as maximum ---no cytotoxicity reported, only one concentration per strain, inadequate positive controls). J Gee, 10/1/85.
EPA One-Liner: Unacceptable. Negative to 1,000 ug/plate.

049 073633 "Amitrole: Aminotriazole Active Ingredient - Salmonella/Microsome Test for Detection of Point-Mutagenic Effects." (Bayer AG, Wuppertal, Report 9339, 8/1/80) Amitrole, batch 208, 97.6%; tested with Salmonella strains TA1535, TA1537, TA98 and TA100, with and without male rat liver S-9 activation; 4 plates per group; 0 (DMSO), 20, 100, 500, 2500 or 12500 µg/plate; duplicate plates for survival; mean value only reported (no individual plate counts or standard deviation); positive controls for activation only; **UNACCEPTABLE,** upgradeable (plate counts). No increase in reversion rate reported and tested to cytotoxicity. Gee, 5/15/89.

Summary: Although no one report/study is acceptable as on file at CDFA, the collective data provide sufficient information on the lack of gene mutation as a result of exposure to amitrole. Note that Record # 073633 is an upgradeable report. Gee, 5/16/89.

MUTAGENICITY, CHROMOSOME

004 002345 "Mutagenicity - Mammalian in vivo and Human Cell Culture Assays: Dominant Lethal Mutation - Mice, DNA synthesis - Mice, Chromosomal Aberrations - Mice, Rats, And Human Lymphocytes." (Union Carbide, 10/83) Summary paragraph on lack of effect of Amitrole on chromosomal aberrations in mice (Record no. 35191), rats (Litton Bionetics, 1973, unpublished) or human lymphocytes in culture (Mutation Res. 40:191-196 (1976)). **UNACCEPTABLE**. J Gee, 11/7/86.
EPA 1-liner: Unacceptable.

021 035191 "Study to Determine the Potential of Amitrole to Induce Dominant Lethal Mutations in HA (ICR) Mice." (Food and Drug Research Labs, Report no. 5502, 2/28/78) Amitrole, 94.59%, in mouse dominant lethal; fed in the diet for 49 consecutive days to 20 males per group at 0, 1 or 10 ppm with TEM as positive control; mated with 2 untreated females weekly for 3 weeks; bone marrow was collected from 5 males/group after returning to the original treatment level for 5 days and cytogenetics scored; no positive effects seen for dominant lethal or chromosomal effects; systemic NOEL = 1 ppm based on body weight; **UNACCEPTABLE** (only two doses with no evidence of m.t.d. for dominant lethal - see doses used in other studies in mice). Record No. 50766 discusses the lack of evidence for dose selection in the files at FDRL). J Gee, 10/1/85.
EPA One-Liner: Unacceptable. Negative for mutagenicity at 1 and 10 ppm for 49 days before mating.

049 073631 "Amitrole: Dominant Lethal Test on the Male Mouse to Evaluate for Mutagenic Effects." (Bayer AG, 3/23/77, translated in 1985, Report no. 6679) Amitrole, no purity stated, batch 143, given by oral gavage to groups of male mice, 49 - 50/group, at 0 (2% aqueous Crempohor) or 1000 mg/kg, single dose; males mated for 12 consecutive 4-day periods to one untreated female for a total of 48 days; no positive control included; no evidence of a dominant lethal effect; **UNACCEPTABLE**, not upgradeable (inadequate dose selection with no evidence of a MTD, no toxic signs reported, no positive control and no analysis of dosing suspension). Gee, 5/12/89.

** 049 073632 "Amitrole: Aminotriazole Active Ingredient - Micronucleus Test on the Mouse to

Evaluate for Mutagenic Effect." (Bayer AG, Wuppertal-Elberfeld, Report No. 11139, 9/13/82, translated in 1985) Amitrole, batch 185, 96.9%; given by oral gavage at 0 (0.5% Cremophor) or 10,000 mg/kg with 5/sex sacrificed at 24 hours for negative and positive (cyclophosphamide) controls and 5/sex in treatment groups at 24, 48 or 72 hours; scored 1000 polychromatic erythrocytes per animal and the ratio of normochromatic per 1000 polychromatic cells; no evidence of toxicity at any time of sacrifice and no adverse effect on bone marrow reported - 5000 mg/kg is the "limit" test; **ACCEPTABLE**. Gee, 5/15/89.

MUTAGENICITY, DNA/OTHER

004 002343 (Union Carbide, 10/83) Summary paragraph of published results with Saccharomyces cerevisiae with negative results for mitotic gene conversion (J. Natl. Canc. Inst. 62:901-909 (1979)). **UNACCEPTABLE**. J Gee, 11/7/86.

**** 019 035187** "Mutagenicity Evaluation of 3-amino-1,2,4-triazole Final Report - in vitro Cellular Transformation in BALB/3T3 Cells." (Litton Bionetics, 10/26/76, Study 2549) Amitrole, 93 to 95 % from Record No. 50764, tested for transforming ability with BALB/3T3 cells at 0, 0.01, 0.05, 0.1, 0.5, 0.6, 1.0, 1.25 or 2.5 mg/ml; cytotoxicity at 10 mg/ml; 72-hour exposure; no activation; exposed for 72 hours, 8-10 replicates per concentration; one of three trials suggests a weak cellular transforming ability; 3-4 plates scored per concentration; initially evaluated as unacceptable based on the lack of purity for test material and definition of scoring for foci. These deficiencies are satisfied by Record Nos. 50764 (purity) and 50765 (scoring) in document 50137-035. **ACCEPTABLE**.
J Gee, 10/1/85 and 7/1/87.
EPA 1-liner: Acceptable.

004 002341 (Union Carbide, 10/83) Summary of 35187 plus other in-vitro studies. J Gee, 11/7/86.

NEUROTOXICITY

Not required at this time.

Volume 045 contains a draft of a document prepared by US EPA addressing thyroid follicular cell carcinogenesis. No worksheet. Gee, 10/17/88.